

Amendments to the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

- 1 – 24. (canceled)
25. (currently amended) An *in vitro* method of increasing targeting frequency of a targeting construct in mouse embryonic stem (ES) cells, comprising:
- (a) constructing a first targeting vector directed to a specific chromosomal location in a mouse ES cell, wherein the first targeting vector comprises a drug resistance gene driven by operably linked to a PGK promoter;
 - (b) introducing the first targeting vector into mouse ES cells *in vitro* to obtain a first group of targeted mouse ES cell[[s]] clones;
 - (c) determining a first targeting efficiency the number of targeted mouse ES cell clones as measured by targeted gene modifications due to targeted, non-random insertions of the first targeting vector in the first group of targeted mouse ES cell[[s]] clones;
 - (d) constructing a second targeting vector directed to the specific chromosomal location of step (a), wherein the second targeting vector comprises a drug resistance gene driven by operably linked to a ubiquitin promoter;
 - (e) introducing the second targeting vector into a second group of mouse ES cells *in vitro* to obtain a second group of targeted mouse ES cell[[s]] clones; and,
 - (f) determining a second targeting efficiency number of targeted mouse ES cell clones as measured by targeted gene modifications due to targeted, non-random insertions of the second targeting vector in the second group of targeted mouse ES cell[[s]] clones, wherein the second targeting efficiency number is proportionately at least two-fold higher than the first targeting efficiency number.
26. (previously presented) The method of claim 25, wherein the ubiquitin promoter is the ubiquitin C promoter.
27. (previously presented) The method of claim 26, wherein the ubiquitin promoter is a human,

mouse, or rat ubiquitin promoter.

28. (previously presented) The method of claim 25, wherein the drug resistance gene encodes neomycin phosphotransferase, hygromycin phosphotransferase, or puromycin acetyl transferase.

29. – 32. (canceled)